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Docket No.: 17243/002001

(PATENT)

#### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of: Melwyn Abreo et al.

Patent No.: 7,763,618

Issued: July 27, 2010

22511

For: PYRIDYL DERIVATIVES AND THEIR USE

AS THERAPEUTIC AGENTS

# REQUEST FOR CERTIFICATE OF CORRECTION PURSUANT TO 37 CFR 1.323

ATTENTION: Certificate of Correction Branch Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dear Sir:

Upon reviewing the above-identified patent, Patentee noted a typographical error which should be corrected.

In the Claims:

In Claim 29, Column 51, Line 47, "- $S(O)_2N(R^{12})_2$ " should read: "- $S(O)_2N(R^{12})_2$ ".

The error was not in the application as filed by applicant; accordingly no fee is required.

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**2**0003/0010

OCT - 4 2010

Patent No.: 7,763,618

Docket No.: 17243/002001

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Also enclosed, as evidence of the error, is a copy of the claims as issued. Patentee respectfully solicits the granting of the requested Certificate of Correction.

Applicant believes no fee is due with this request. However, if a fee is due, please charge our Deposit Account No. 50-0591, under Order No. 17243/002001.

Dated: October 4, 2010

Respectfully submitted,

Rν

T. Chyau Liang, Ph.D. Registration No.: 48,885

OSHA · LIANG LLP Two Houston Center

909 Fannin Street, Suite 3500

30 Chran L. - I

Houston, Texas 77010

(713) 228-8600

(713) 228-8778 (Fax)

Attorney for Applicants

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(Also Farm P10-1950)

## UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 1

PATENT NO.

7,763,618

APPLICATION NO. :

10/566,857

ISSUE DATE

July 27, 2010

INVENTOR(S)

Melwyn Abreo et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims:

In Claim 29, Column 51, Line 47, "-S(O)<sub>2</sub>N(R<sup>12</sup>)2" should read;

"- $S(O)_2N(R^{12})_2$ ".

MAILING ADDRESS OF SENDER (Please do not use customer number below): T. Chyau Liang, Ph.D. OSHA LIANG I.LP Two Houston Center 909 Fannin Street, Sulte 3500

Houston, Texas 77010

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nate mitochondria and cullular debris. The supernatant is filtered through a 3-layer cheesecloth and centrifuged at 105, 000xg for 60 min. The microsomal pollet is gently resuspended in the same homogenization solution with a small glass/tefion homogenizer and stored at -70° C. The absence 5 of mitochondrial contamination is enzymatically assessed. The protein concentration is measured using bovine serum albumin as the standard.

Incubation of Mouse Liver Microsomes with Test Courpounds:

Reactions are started by adding 2 mg of microsomal protein to pre-incubated tubes containing 0.20 µCi of the substrate fatty acid (1-14C pulmitic acid) at a final concentration 15 of 33.3 µM in 1.5 ml of homogenization solution, containing 42 mM NaF, 0.33 mM niacinamide, 1.6 mM ATP, 1.0 mM NAIDII, 0.1 mM coenzyme A and a 10 µM concentration of test compound. The tubes are vortexed vigorously and after 15 min incubation in a shaking water buth (37° C.), the reac- 20 tions are stopped and futly acids are analyzed.

l'atty acida are analyzed as follows: The reaction mixture is saponified with 10% KOH to obtain free fatty acids which are further methylated using BP3 in methanol. The fatty acid 25 methyl caters are analyzed by high performance liquid chinmatography (HPLC) using a Hewlett Packard 1090, Series II chromatograph equipped with a diode array detector set at 205 nm, a radioisotope detector (Model 171, Beckman, Calif.) with a solid scintillation cartridge (97% efficiency for 30 14C-detection) and a reverse-phase ODS (C-18) Beckman column (250 mmx4.6 mm i.d.; 5 µm particle size) attached to ирго-column with и µBondapak (!-1X (Beckman) insert. Fatty acid methyl esters are separated isocratically with acotonitrile/water (95:5 v:v) at a flow rate of 1 mL/min and are 35 identified by comparison with authentic standards. Alternatively, fatty acid methyl esters may be analyzed by capillary column gas-chromatography (GC) or Thin Layer Chromatography (TLC).

Those skilled in the art are aware of a variety of modificathous to this assay that can be useful for measuring inhibition of stearoyl-CoA desaturase activity in microsomes by test compounds.

Representative compounds of the invention showed activ- 45 ity as inhibitors of SCD when tested in this assay. The activity was defined in terms of % SCID enzyme activity remaining at the desired concentration of the test compound.

All of the U.S. patents, U.S. patent application publications, U.S. putent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated berein by reference, in their entirety.

From the foregoing it will be appreciated that, although 55 specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

The invention channel is:

1. A method of inhibiting human stearcyl-CoA desaturase 65 in vitro (hSCD) activity comprising contacting a source of hSCD with a compound of formula (I):

$$R^{2}-W \xrightarrow{R^{4}} R^{10} \xrightarrow{R^{10}} R^{10} R^{7} R^{7} U - V - R^{3}$$

$$R^{6} R^{6} R^{6} R^{8} R^{8}$$

$$R^{6} R^{6} R^{8} R^{8}$$

$$R^{6} R^{6} R^{8} R^{8} R^{8}$$

$$R^{6} R^{6} R^{8} R^{8} R^{8}$$

$$R^{6} R^{6} R^{8} R^{8}$$

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wherein:

x and y are each independently 1; W is  $-C(O)N(R^1)$ —or  $-N(R^1)C(O)$ —; V is -C(O)—;

each R1 is independently selected from the group consisting of hydrogen, C1-C12alkyl, C2-C12hydroxyalkyl, C4-C12cycloalkylalkyl and C7-C19aralkyl;

R2 is selected from the group consisting of C1-C12alkyl, C<sub>2</sub>-C<sub>12</sub>hydroxyslkyl, C<sub>2</sub>-C<sub>12</sub>alkoxyslkyl,  $C_x$ - $C_y$ , alkenyl, C2-C12liydroxyulkenyl, C<sub>3</sub>-C<sub>12</sub>cycloalkyl, Ca-Cacyclonlkylulkyl, C7-C19aralkyl, C<sub>3</sub>-C<sub>12</sub>heterocyclyl, C3-C12heterocyclylalkyl, C<sub>1</sub>-C<sub>12</sub>hetercaryl, C<sub>3</sub>-C<sub>12</sub>heteroarylalkyl;

R" is phenyl or naphthyt;

R4, R5 and R6 are each independently selected from hydrogen, fluoro, chioro, methyl, methoxy, trifluoromethyl, cyano, nitro or  $-N(R^{13})_2$ ;  $R^7$ ,  $R^{9}$ ,  $R^{8}$ ,  $R^{9}$ ,  $R^{9}$ ,  $R^{9}$ ,  $R^{9}$ ,  $R^{10}$  and  $R^{10}$  are each independent

dently selected from hydrogen or C,-C,alkyl;

each  $\mathbb{R}^{13}$  is independently selected from hydrogen or C<sub>3</sub>-C<sub>6</sub>alkyl;

a storeoisomer, enantiomer or tautomer thereof, or a pharmaceutically acceptable salt thereof.

2. A method of alleviating a disease or condition mediated 40 by stearcyl-CoA desaturase (SCI)) in a mammal, wherein the method comprises administering to the manual in need thereof a therapeutically effective amount of a compound of formula (1):

x and y are each independently 1;

W is  $-C(O)N(R^1)$ — or  $-N(R^1)C(O)$ ;

V is C(O)--;

each R4 is independently selected from the group consisting of hydrogen,  $C_1$ - $C_{12}$ alkyl,  $C_3$ - $C_{12}$ lydroxyalkyl,  $C_4$ - $C_{12}$ cycloalkylalkyl and  $C_7$ - $C_{13}$ aralkyl;

R2 is selected from the group consisting of C1-C12alkyl C<sub>2</sub>-C<sub>12</sub>hydroxyalkyl, C<sub>2</sub>-C<sub>12</sub>alkoxyalkyl, C<sub>2</sub>-C<sub>12</sub>alkeuyl, C2-C12hydroxyalkenyl, C4 C12 cyclonlkylulkyl, C3-C12cycloalkyl,

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C<sub>2</sub>-C<sub>13</sub>umlkyl, C3-C12heterocyclyl, C3.C12heterocyclylalkyl, C1-C12heteroaryl, C3 · C12 heterouryfulkyl;

R3 is phenyl or naphthyl;

 ${\rm K}^4, {\rm K}^5$  and  ${\rm K}^6$  are each independently selected from hydrogen, fluoro, chloro, methyl, methoxy, (rifluoromethyl, eyuno, nitro or  $-N(R^{10})_2$ ;  $R^7$ ,  $R^{9n}$ ,  $R^{8n}$ ,  $R^{10}$  and  $R^{10n}$  are each indepen-

dently selected from hydrogen or C<sub>1</sub>-C<sub>3</sub>alkyl; and each R<sup>13</sup> is independently selected from hydrogen or <sup>10</sup>

C1-C6alkyl;

a stereoisomer, enantiomer or tautomer thereof, or a pharmaceutically acceptable salt thereof,

and wherein the disease or condition is selected from the group consisting of Type II diabetes, impaired glucose 15 tolerance, insulin resistance, obesity, fatty liver, nonalcoholic steatchepatitis, dyslipidemia, acne, and my combination of these.

3. The method of claim 2 wherein the mammal is a human.

4. The method of claim 3, wherein the disease or condition 20 is Type II diabetes.

5. The method of claim 3, wherein the discuse or condition

6. The method of claim 3, wherein the disease or condition 25 is insulin resistance

7. The method of claim 3, wherein the disease or condition is fatty liver.

8. The method of claim 3, wherein the disease or condition is non-alcoholic steatchepatitis.

9. A compound of formula (Ha):

wherein:

x and y are each independently 1;

R' is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>1</sub>-nlkyl, C2-C12hydroxyalkyl, C4 C12 eyelculkylulkyl und C2-C12 aralkyl;

R<sup>2</sup> is selected from the group consisting of C<sub>7</sub>-C<sub>12</sub>ulkyl, C<sub>3</sub>-C<sub>12</sub>alkenyl, C<sub>7</sub>-C<sub>12</sub>lrydroxyalkyl, C<sub>1</sub>-C<sub>12</sub>alkoxyalkyl, C<sub>3</sub>-C<sub>12</sub>lrydroxyalkenyl, Ca-C12cycloalkylalkyl,  $C_3$ - $C_{12}$ cycloalkyl, Cipuralkyl, Ci-Ci heteroaryl, C3-C12heterocyclylalkyl and C3-C12heteroarylalkyl, provided that R2 is not pyrazinyl, pyridinonyl, pyrrolidinonyl or imidazolyl; R' is plicuyl or nuphthyl;

 $R^4, R^5$  and  $R^6$  are each independently selected from hydrogen, fluoro, chloro, methyl, methoxy, trifluoromethyl,

cyano, nitro or  $-N(\mathbb{R}^{13})_2$ ;  $\mathbb{R}^7$ ,  $\mathbb{R}^{7a}$ ,  $\mathbb{R}^8$ ,  $\mathbb{R}^{4a}$ ,  $\mathbb{R}^4$ ,  $\mathbb{R}^4$ ,  $\mathbb{R}^{4a}$ ,  $\mathbb{R}^4$ ,  $\mathbb{R}^{4a}$ dently selected from hydrogen or C,-C, alkyl;

each R15 is independently selected from hydrogen or  $C_1$ - $C_6$ alkyl;

a stereoisomer, ensutiomer or tautomer thereof, or a plagunceutically acceptable salt thereof

10. The compound of claim 9 wherein:

x and y are each 1;

R1 is hydrogen or C1-C5alkyl;

 $\mathbb{R}^2$  is selected from the group consisting of  $C_7$ - $C_{12}$ alkyl, C<sub>2</sub>-C<sub>12</sub>alkenyl, C<sub>2</sub>-C<sub>12</sub>alkoxyalkyl, C<sub>7</sub>-C<sub>12</sub>hydroxyalkyl, C<sub>3</sub>-C<sub>12</sub>hydroxyalkenyl, C4-C12cycloalkylalkyl, C<sub>3</sub>-C<sub>12</sub>cycloslkyl,  $C_3$ - $C_{12}$ heterocyclyfulkyl, malkyl, تورت C<sub>3</sub>-C<sub>12</sub>heterourylalkyl;

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is plumyl or maphthyl;

 $R^4, R^5$  and  $R^6$  are each hydrogen; and  $R^7, R^{7\alpha}, R^2, R^{8\alpha}, R^9, R^{9\alpha}, R^{10}$ , and  $R^{10\alpha}$  are each hydrogen. 11. A method of alleviating a discuse or condition mediated by stearnyl-CoA desaturase (SCD) in a mannial, wherein the method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 9, and wherein the disease or condition is selected from the group consisting of Type II diabetes, impaired glucose tolerance, insulin resistance, obesity, fatty liver, non-alcoholic steatchepatitis, dyslipidemia, acne, and any combination of

12. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim 9.

13. A compound of formula (IIb):

$$\mathbb{R}^{1} \xrightarrow{\mathbb{R}^{4}} \mathbb{R}^{3} \xrightarrow{\mathbb{R}^{10e}} \mathbb{R}^{7} \mathbb{R}^{7e}$$

$$\mathbb{R}^{2} \xrightarrow{\mathbb{R}^{4}} \mathbb{R}^{4} \xrightarrow{\mathbb{R}^{4}} \mathbb{R}^{3}$$

$$\mathbb{R}^{6} \xrightarrow{\mathbb{R}^{2e}} \mathbb{R}^{4e}$$

$$\mathbb{R}^{3}$$

$$\mathbb{R}^{4} \xrightarrow{\mathbb{R}^{3}} \mathbb{R}^{4e}$$

$$\mathbb{R}^{3}$$

$$\mathbb{R}^{4} \xrightarrow{\mathbb{R}^{3}} \mathbb{R}^{4e}$$

$$\mathbb{R}^{3}$$

$$\mathbb{R}^{4} \xrightarrow{\mathbb{R}^{3}} \mathbb{R}^{4e}$$

$$\mathbb{R}^{3} \xrightarrow{\mathbb{R}^{4}} \mathbb{R}^{4e}$$

wherein:

x and y are each independently 1;

R1 is selected from the group consisting of hydrogen,  $C_1$ - $C_{12}$ alkyl, C2-C12hydroxyulkyl,

C4-C12cyclosikylalkyl and C7-C19arolkyl; R2 is selected from the group consisting of C1-C12alkyl,

C<sub>2</sub>-C<sub>12</sub>alkenyl, C<sub>2</sub>-C<sub>12</sub>hydroxyalkyl,  $C_2$ - $C_{12}$ hydroxyalkenyl, C<sub>1</sub>-C<sub>6</sub>alkoxy,  $C_3$ - $C_{12}$ lykoxyalkyl,  $C_3$ - $C_{12}$ cycloalkyl,  $C_4$ - $C_{12}$ cycloalkyl,  $C_4$ - $C_{12}$ cycloalkylalkyl,  $C_7$ - $C_{10}$ aralkyl,  $C_3$ - $C_{12}$  heterocyclyl,  $C_3$ - $C_{12}$ hoterocyclylalkyl,  $C_1$ - $C_{12}$ heteroaryl and C<sub>5</sub>-C<sub>12</sub>heterosryhikyl;

or R2 is phonyl optionally substituted with one or more substituents selected from halo and C<sub>1</sub>-C<sub>8</sub>tribuloulkyl;

R3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, cyano, rdiro, hydroxy,  $C_1$ - $C_6$ ulkyl,  $C_1$ - $C_6$ trihuloulkyl,  $C_1$ - $C_6$ trihuloulkoxy,  $C_1$ - $C_6$ dikylsulfonyl,  $N(R^{12})_2$ ,  $-CC(C)R^{12}$ ,  $-C(C)OR^{12}$ ,  $S(O)_2N(R^{12})_3$ , cycloalkyl, lieterocyclyl, helerosryl and hoterosrylcy-cloalkyl, provided that R<sup>3</sup> is not phenyl substituted with optionally substituted thirmyl;

R\*, R\* and R\* are each independently selected from hydro-

C1-C6alkyl, C1-C6cyclusikyl, aryl or smikyl; and

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49 each R<sup>13</sup> is independently selected from hydrogen or

a stereoisomer, enantiomer or tautomer thereof, or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13 wherein:

x and y are each 1;

R' is hydrogen or C,-C, alkyl;

R2 is selected from the group consisting of C1-C12alkyl, C<sub>2</sub>-C<sub>12</sub>alkenyl, C2-C12hydroxyalkyl, Ca-Cashydroxyalkenyl,  $C_1 \cdot C_6$ alkoxy, 10 C<sub>3</sub> C<sub>12</sub>cycloalkyl, C<sub>2</sub>-C<sub>12</sub>alkoxyalkyl, C4-C12cycloalkylalkyl, C7-C19aralkyl, C3-C12 heterncyclyl, C3-C12heterocyclylalkyl, C1-C12heteroaryl and -C<sub>12</sub>heterourylalkyl;

or R2 is phenyl optionally substituted with one or more 15 substituents selected from halo or C1-Catribaloalkyl;

R3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, hydroxy,  $C_1$ - $C_0$ alkyl,  $C_1$ - $C_0$ tribalo,  $C_1$ - $C_0$ tribaloalkoxy,  $C_1$ - $C_0$ alkylsul tonyl, —N(I—OC(O)R<sup>12</sup>, —C(O)OR<sup>12</sup> and —S(O)<sub>2</sub>N(R<sup>12</sup>)<sub>2</sub>; C<sub>1</sub>-C<sub>c</sub>tribalnalkyl, -N(!R<sup>12</sup>)<sub>2</sub>, 20 R4, R5 and R6 are each hydrogen;

R7, R7a, R8, R8a, R9, R9a, R10, and R111a are each hydrogen; and

each R12 is independently selected from hydrogen, 25 C1-Catkyl, C3-Cacyclonikyl, myl or malkyl.

15. The compound of claim 14 wherein:

R2 is C<sub>2</sub>-C<sub>1</sub>, aralkyl optionally substituted by one or more substituents selected from the group consisting of halo,  $C_1$ - $C_3$ ulkyl and  $C_1$ - $C_6$ tribaloulkyl; and

R3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>trihaloalkyl and C<sub>1</sub>-C<sub>6</sub>trihaloalkoxy.

16. The compound of claim 15 selected from the group

consisting of the following: 3-(4-Fluoro-phenyl)-N-[5-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-pyridin-2-yl]-propiomunide;

4-Phenyl-N-{5-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-pyrklin-2-yl}-butyramide;

4-(4-Fluoro-phenyl)-N-{5-[4-(2-trifluoromethyl-benzoyl)-piperazin-1-yl]-pyridin-2-yl]-butyramide; and

3-Phenyl N (5-[4-(2-trifluoromethyl-benzoyl)-pipemzin-1-yl]-pyridin-2-yl}-propionamide.

17. The compound of claim 14 wherein:

 $R^2$  is  $C_1$ - $C_{12}$ alkyl or  $C_2$ - $C_{12}$ alkenyl; and

R3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, C1-Coulkyl, C1-Cotribaloalkyl and C1-Cotribaloalkoxy. 18. The compound of claim 17 selected from the group 50

consisting of the following:

Hexausic ucid {5-[4-(2-trifluoromethyl-henznyl)-piper-azin-1-yl]-pyridin-2-yl]-mnide; Heptunoic acid {5-[4-(2-trifluoromethyl-benzoyl)-piper-

uzin-1-yl]-pyridin-2-yl}-amide; and 5-Methylpentanoic [5-[4-(2-trifluoromethyl-benzoyl)-piperuzin-1yl]-pyridin-2-yl]-umide.

19. The compound of claim 14 wherein:

R<sup>2</sup> is C<sub>3</sub>-C<sub>12</sub>heteroarylalkyl optionally substituted by one or more substituents selected from the group consisting 60 of halo, C1 Calkyl and C1-Catribal calkyl; and

R3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, C1 Conlkyl, C1-Cotribaloulkyl und C1-Cotribuloulkoxy.

20. The compound of claim 19, namely, 3-Pyridin-3-yl-N- 65 {5 [4 (2 trifluoromethyl-benzoyl)-piperazin-1-yl]-pyridin-2-yl }-propionamide.

21. The compound of claim 14 wherein:

R2 is phenyl optionally substituted with one or more substituents selected from halo and C1-C6trihaloalkyl; and R3 is phenyl optionally substituted by one or more substitucan's selected from the group consisting of hulo,  $C_1$ - $C_6$ nlkyl,  $C_1$ - $C_6$ trihaloulkyl and  $C_1$ - $C_6$ trihaloulkoxy.

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22. The compound of claim 21, namely, 4-Fluoro-N-{5-[4-(2-trifluoromethylbenzoyl)piperazin-1-yl]pyridin-2-

yi}benzamide.

23. A method of alleviating a disease or condition mediated by stearoyl-CoA desaturase (SCD) in a mammal, wherein the method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 13, wherein the discuse or condition is selected from the group consisting of Type II diabetes, impaired glucose telerunce, insulin resistance, obesity, fatty liver, non-alcoholic steatohepatitis, dyslipidemia, acne, and any combination of these.

24. A phanuaceutical composition comprising a pharmaccutically acceptable excipient and a therapeutically effective amount of a compound of claim 13.

25. A compound of formula (Via):

(Vla)

a and y are each independently 1;

R1 is selected from the group consisting of hydrogen,  $C_1$ - $C_{12}$ alkyl, C2-C12hydroxyalkyl, C4-C12cycloalkylalkyl and C7-C12aralkyl;

R? is selected from the group consisting of Cy-Cyalkyl, C<sub>2</sub>-C<sub>12</sub>hydroxyalkyl, C<sub>3</sub>-C<sub>12</sub>hydroxyalkenyl, C3-C12ulkenyl, C2-C120lloxyalkyl, C<sub>2</sub>-C<sub>12</sub>man, C<sub>4</sub>-C<sub>12</sub>cyclom, C<sub>5</sub>-C<sub>12</sub>cyclom, C<sub>7</sub>-C<sub>12</sub>cyclom, C<sub>7</sub>-C<sub>12</sub>heterocyclylalkyl, C4-C12cycloalkylalkyl, C3-C12heteroarylalkyl;

R3 is phenyl or naphthyl;

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are each independently selected from hydrogen, fluoro, chloro, methyl, methoxy, trifluoromethyl, cyano, nitro or -N(R13)2;

 $R^7$ ,  $R^{7\alpha}$ ,  $R^8$ ,  $R^{8\alpha}$ ,  $R^9$ ,  $R^{9\alpha}$ ,  $R^{10}$ , and  $R^{10\alpha}$  are each independently selected from hydrogen or C1-C3alkyl;

each R13 is independently selected from hydrogen or C<sub>1</sub>-C<sub>6</sub>nlkyl;

including a stereoisomer, enantiomer or tautomer thereof, or a pharmaceutically acceptable salt thereof.

26. The compound of claim 25 wherein:

x and y are each 1;

R1 is hydrogen or C1-C68lkyl;

 $R^2$  is selected from the group consisting of  $C_{\gamma}$ - $C_{12}$ alkyl, C,-C<sub>12</sub>hydroxyalkyl, C,-C, hydroxyalkenyl, C<sub>2</sub>-C<sub>12</sub>alkenyl,  $C_x$ - $C_{xalkoxyalkyl}$ , C<sub>3</sub>-C<sub>12</sub>cycloalkyl, C<sub>4</sub>-C<sub>12</sub>cycloalkylalkyl, C<sub>10</sub>aralkyl, C<sub>3</sub>-C<sub>12</sub>heterocyclylalkyl, C3-C12heteroorylalkyl;

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R<sup>5</sup> is phenyl or naphthyl; R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are each hydrogen; and

R',  $R'^a$ ,  $R^a$ ,  $R^{aa}$ ,  $R^a$ ,  $R^{aa}$ ,  $R^{aa}$ ,  $R^{aa}$ ,  $R^{aa}$ , and  $R^{10a}$  are each hydrogen.  $27.\Lambda$  method of alleviating a disease or condition mediated by stearoyl-CoA desaturese (SCD) in a mammal, wherein the 5 method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 25, and wherein the disease or condition is selected from the group consisting of Type II diabetes, impaired glucose tolerance, insulin resistance, obesity, fatty liver, non-alcoholic 10 steatoheputitis, dyslipidemis, sene, and any combination of

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28. A pharmaceutical composition comprising a pharmaccutically acceptable excipient and a theraportically effective amount of a compound of claim 25.

29. A compound of formula (VIb);

$$\mathbb{R}^{2} = \mathbb{N} = \mathbb{R}^{5} \xrightarrow{\mathbb{R}^{100}} \mathbb{R}^{10} \times \mathbb{R}^{7} \times \mathbb{R}^{10} \times$$

x and y are each independently 1;

each R1 is independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>1</sub>,alkyl, C<sub>2</sub>-C<sub>12</sub>hydroxyalkyl, C<sub>4</sub>-C<sub>12</sub>cycloalkylalkyl and C<sub>7</sub>-C<sub>10</sub>aralkyl;

R<sup>2</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>12</sub>alkyl, 35 C<sub>2</sub>-C<sub>12</sub>alkenyl,  $C_2$ - $C_{12}$ hydroxyalkyl,  $C_3$ - $C_{12}$ alkoxyalkyl,  $C_4$ - $C_{12}$ eyeloulkylulkyl, uryl, C2-C12hydroxyalkenyl, C<sub>3</sub>-C<sub>12</sub>cycloalkyl,  $C_7$ - $C_{19}$ aralkyl, C<sub>3</sub>-C<sub>12</sub>heterocyclyl, C<sub>3</sub>-C<sub>12</sub>heterocyclylalkyl,  $C_1$ - $C_{12}$ heteroaryl กบติ 40 C<sub>1</sub>-C<sub>12</sub>heteroarylalkyl;

R3 is nuplithyl or plicityl, each optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, hydroxy,  $C_1$ - $C_0$ ilkyl,  $C_1$ - $C_0$ trihaloalkyl,  $C_1$ - $C_1$ - $C_1$ - $C_1$ - $C_1$ - $C_2$ - $C_2$ - $C_1$ - $C_2$ - $C_$ phenyl substituted with optionally substituted thienyl, and provided that when R3 is nuphthyl, R2 cun not be 50 C1-C6alkyl, C2-C6hydroxyalkyl or phenyl substituted by amino;

 ${
m R}^4, {
m R}^3$  and  ${
m R}^6$  are each independently selected from hydrogen, fluoro, chloro, methyl, methoxy, trifluoromethyl, cyano, nitro or —N(R<sup>12</sup>)<sub>2</sub>;
R<sup>7</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>8</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>10</sup>, and R<sup>10</sup> are each independently selected from hydrogen or C<sub>1</sub>-C<sub>2</sub>alkyl; cach R<sup>12</sup> is independently selected from hydrogen,

C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, aryl or aralkyl; and

each R13 is independently selected from hydrogen or 60  $C_1 \cdot C_{\delta}$ alkyl;

a stereoisomer, enantiomer or tautomer thereof, or a pharmaceutically acceptable salt thereof,

30. The compound of claim 29 wherein: x and y are each 1;

 $R^1$  is hydrogen or  $C_1$ - $C_6$ alkyl;

R2 is selected from the group consisting of C1-C12alkyl, C<sub>2</sub>-C<sub>12</sub>hydroxyalkyl, C<sub>2</sub>-C<sub>12</sub>alkoxyalkyl,  $C_2$ - $C_{12}$ alkenyl, C2-C12hydroxyalkenyl, C3-C12cycloalkyl, C<sub>4</sub>-C<sub>12</sub>cycloalkylalkyl,  $C_3 C_{12}$ hetemcyclyl, C7-C19Brulkyl, C<sub>3</sub>-C<sub>12</sub>heterocyclylalkyl, C<sub>1</sub>-C<sub>12</sub>hetemaryl

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C<sub>3</sub>-C<sub>12</sub>heterourylulkyl; R3 is naphthyl or phonyl, each optionally substituted by one or more substituents selected from the group consisting

of halo, cyano, nitro, hydroxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>trihaloalkory, C<sub>1</sub>-C<sub>6</sub>trihaloalkory, C<sub>1</sub>-C<sub>6</sub>ulkylsulfonyl, —N(R<sup>12</sup>)<sub>2</sub>, —OC(O)R<sup>12</sup>, —C(O) OR<sup>12</sup> or —S(O)<sub>2</sub>N(R<sup>12</sup>)<sub>2</sub>; R<sup>3</sup>, R<sup>3</sup> and R<sup>4</sup> are each hydrogen; R<sup>7</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>9</sup>, R<sup>10</sup>, and R<sup>100</sup> are each hydrogen;

cach R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>cycloalkyl, aryl or aralkyl.

31. The compound of claim 30 wherein:

R2 is C7-C12 aralkyl optionally substituted by one or more substituents selected from the group consisting of halo,  $C_1$ - $C_3$ elkyl and  $C_1$ - $C_6$ tribaloalkyl; and

R3 is phonyl optionally substituted by one or more substituunts sulceted from the group consisting of halo,  $C_1$ - $C_6$ ulkyl,  $C_1$ - $C_6$ trihuloalkyl and  $C_1$ - $C_6$ trihaloalkoxy. 32. The compound of claim 31 selected from the group

consisting of the following:

5-[4-(2-Trifluoromethyl-benzoyl)-piperazin-1-yl]-pyridine-2-carboxylic scid (3-phonyl-propyl)-amide;

5-[4-(2-Trifluoromethyl-benzayl)-piperazin-1-yll-pyridine-2-curboxylic acid phenethyl-amide;

5-[4-(2-Trifluoromethylbenzoyl)piperuzin-1-yl]pyridine-2-carboxylic acld [2-(4-fluom-phenyl)athyl]amide;

5-[4-(2-Trifluoromethyl-benzoyl)-piperazin-1-yl]-pyridinc-2-carboxylic acid [3-(4-fluoro-phenyl)-propyl]-

5-[4-(2-Trifluoromethyl-benzoyl)-piperazin-1-yl]-pyri-dine-2-carboxylic soid 4-trifluoromethyl-benzylamide;

5-[4-(2-Triffluoromothyl-henzoyl)-piperazin-1-yl]-pyridinc-2-carboxylic acid [3-(4-trifluoromethyl-phenyl)propyl]-amide; and

5-[4-(2-Trifluoromethyl-benzoyl)-piperazin-1-yl]-pyridine-2-curboxylic acid [2-(4-trifluoromethyl-phenyl)-

The compound of claim 30 wherein;

 $\mathbb{R}^2$  is  $C_1$ - $C_{12}$ alkyl or  $C_2$ - $C_{12}$ alkenyl; and  $\mathbb{R}^3$  is phenyl optionally substituted by one or more substituents selected from the group consisting of halo,  $C_1$ - $C_6$ ulkyl,  $C_1$ - $C_6$ tribuloulkyl and  $C_1$ - $C_6$ tribuloulkyl. 34. The compound of claim 33 selected from the group

consisting of the following:

5-[4-(2-Triffnoromethyl-benzoyl)-piperazin-1-yl]-pyridinc-2-carboxylic acid (3-methyl-butyl)-amide;

5-[4-(2-Trifluorome(hyl-benzoyl)-piperazin-1-yl]-pyridine-2-curboxylie acid hexylamide;

5 [4 (2 Trifluoromethyl-benzoyl)-pipunzin-l-yl]-pyridine-2-carboxylic acid pentylamide;

5-[4-(4-Phioro-2-triffuoromethyl-benzoyl)-pipeniziu-1yl]-pyridino-2-carhoxylic scid (3-methyl-butyl)-amide;

5-[4-(5-Pluoro-2-trifluoromethyl-benzoyl)-piperazin-1yl]-pyridine-2-carboxylic acid (3-methyl-butyl)-amide. 35. The compound of claim 30 wherein:

R2 is C3-C12cycloalkyl or C4-C12cycloulkylalkyl; and R3 is phenyl optionally substituted by one or more substituants selected from the group consisting of halo, C1-Costkyl, C1-Cotribatoalkyl and C1-Cotribaloalkoxy.

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- 36. The compound of claim 35 selected from the group consisting of the following:
  - 5-[4-(2-Triffuoromethylbenzoyl)piperazin-1-yl]pyridine-
  - 2-carboxylic acid (3-cyclohexyl-propyl)umide; 5-[4-(6-Trifluoromethyl-cyclohexa-1,3-diencearbonyl)piperazin-1-yll-pyridine-2-carboxylic acid (2-cyclo-hexyl-ethyl)-amide; and
  - 5-[4-(2-Trifluoromethyl-benzoyl)-piperazin-1-yl]-pyridine-2-carboxylic acid cyclohexylmethyl-amide.
  - 37. The compound of claim 30 wherein:
  - R<sup>2</sup> Is C<sub>3</sub>-C<sub>12</sub>heterocyclylalkyl optionally substituted by one or more substituents selected from the group con-Sisting of halo, cyano, nitro, hydroxy, C<sub>1</sub>-C<sub>0</sub>ulkyl, C<sub>1</sub>-C<sub>0</sub>tribaloulkyl, C<sub>1</sub>-C<sub>0</sub>tri
- R3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>trihaloalkyl and C<sub>1</sub>-C<sub>6</sub>trihaloalkoxy; and
- euch R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, aryl or aratkyl.

  38. The compound of claim 37 wherein R<sup>2</sup> is 2-piperazipylethyl optionally substituted by C(O)OR<sup>12</sup>.
- 39. The compound of claim 38, namely, 4-[2-({5-[4-(2- 25 Trilluoromethyl-benzoyl)-piperazin-1-yl]-pyridine-2-carbonyl)-muino)-clhylj-pipcrazine-1-carboxylic acid tert-butyl

- 40. The compound of claim 30 wherein:
- R3 is C7-C12aralkyl optionally substituted by one or more substituents selected from the group consisting of halo, C1-C3alkyl and C1-Cstribuloulkyl; and
- R3 is naphthyl optionally substituted by one or more substituents selected from the group consisting of halo, C1-Csalkyl, C1-Cstribuloulkyl and C1-Cstribaloalkoxy.
- 41. The compound of claim 40 selected from the group 10 consisting of the following:
  - 5-[4-(Naphthuleue-1-curbonyl)-pipcrazin-1-yl]-pyridine-2-carboxylic acid (3-phenyl-propyl)-unide; and
  - 5-[4-(Naphthaleae-1-curbonyl)pipcrazin-1-yl]pyrldine-2carboxylic acid phenethylamide.
  - 42. A method of alloviating a disease or condition mediated by stearoyl-CoA desaturese (SCD) in a mammal, wherein the method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 29, wherein the disease or condition is selected from the group consisting of Type II dishetes, impaired glucose tolerance, insulin resistance, obesity, fatty liver, non-atcoholic steatohepatitis, dyslipidemia, acne, and any combination of these.
- 43. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of chim 29.

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